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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Monty Krieger, Susan L. Acton, and Antillio Rigotti

Serial No: 08/765,108 Art Unit: 1646

Filed: March 27, 1997 Examiner: J. Ulm

For: *CLASS BI AND CI SCAVENGER RECEPTORS*

Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF APPEAL BRIEF

Sir:

In response to the Office Action finally rejecting claims 9-15, 19-22, and 44-50, mailed March 19, 1998, maintained in the Advisory Action mailed August 3, 1998, and further to the Notice of Appeal mailed August 11, 1998, enclosed is an Appeal Brief, in triplicate, along with a check in the amount of $300.00 which is the fee for filing of an Appeal Brief by a large entity. Submitted with this Appeal Brief is a Petition for a four month extension of time and the appropriate fee for a large entity, and an Amendment cancelling claims 9 and 10.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge any additional fees to

MIT 6620 CIP
20220/422

Deposit Account No. 01-2507. To facilitate this process, a duplicate of this Transmittal of Appeal Brief is enclosed.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: February 11, 1999
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CERTIFICATE OF MAILING UNDER 37 CFR § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Patrea L. Pabst

Date: February 11, 1999

FORM PTO-1083

D / February 11, 1999
C Docket No. MIT 6620 CIP

In re application of: Monty Krieger, Susan L. Acton, and Antillio Rigotti

Serial No.: 08/765,108
Filed: March 27, 1997
For: *CLASS BI AND CI SCAVENGER RECEPTORS*

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

~~Sir~~:

Transmitted herewith is an amendment in the above-identified application.

☐ Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.

☐ A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.

☐ No additional fee is required.

The fee has been calculated as shown below:

	(Col. 1)		(Col. 2)	(Col. 3)		SMALL ENTITY			OTHER THAN A SMALL ENTITY	
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE	ADDIT. FEE		RATE	ADDIT. FEE
TOTAL	16	MINUS	20	= 0		X =	$		x =	$0
INDEP	5	MINUS	6	= 0		x =	$		x =	$0
☐☒ FIRST PRESENTATION OF MULTIPLE DEP. CLAIM						+	$		+	$0
					TOTAL ADDIT. FEE		$	or	TOTAL	$0

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.

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The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col.1 of a prior amendment or the number of claims originally filed.

☐ Please charge my Deposit Account No. 01-2507 in the amount of $_____. A duplicate copy of this sheet is attached.

☒ Check in the amount of $1,660.00 is attached.

☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 01-2507. A duplicate copy of this sheet is enclosed.

☒ Any additional filing fees under 37 CFR 1.16 for the presentation of extra claims.

☒ Any patent application processing fees under 37 CFR 1.17.

Respectfully submitted,

Patrea L. Pabst, Reg. No. 31,284

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Monty Krieger and Susan L. Acton

Serial No.: 08/765,108 Group Art Unit: 1646

Filed: March 27, 1997 Examiner: J. Ulm

For: CLASS BI AND CI SCAVENGER RECEPTORS

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 9-15, 19-22, and 44-50 in the Office Action mailed March 19, 1998, maintained in the Advisory Action mailed August 3, 1998 in the above-identified patent application. A Notice of Appeal was mailed on August 11, 1998. A check in the amount of $ 300.00 for the filing of this Appeal Brief, a Petition to Extend the Period for Response for Four Months, to and including February 11, 1999, and the appropriate fee for a large entity are also enclosed.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Massachusetts Institute of Technology, Cambridge, Massachusetts, the assignee.

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(2) RELATED APPEALS AND INTERFERENCES

There is a related Appeal known to Appellants, the undersigned, or Appellants' assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal. An appeal is pending in U.S. Serial No.: 08/265,428 entitled "Class BI and CI Scavenger Receptors" filed June 23, 1994 by Monty Krieger and Susan Acton.

Please note that the inventorship of this application was amended in the Preliminary Amendment mailed December 23, 1996, cancelling claims 1-8 and 23-43, since Attilio Rigotti is not an inventor of the remaining claims. The inventorship of the claims in this application and in the related case on appeal is the same.

(3) STATUS OF CLAIMS ON APPEAL

Claims 9-15, 19-22, and 44-50 are pending. An Amendment cancelling claims 9 and 10 accompanies this Appeal Brief. Claims 1-8 and 23-43 were cancelled in the Amendment mailed December 23, 1996. Claims 16-18 were cancelled in an Amendment mailed December 29, 1997. Claims 11-15, 19-22, and 44-50 are on appeal. The text of each claim on appeal, as amended, is set forth in the Appendix I to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment mailed July 20, 1998. This amendment was to be entered upon filing of an appeal, as stated in the Advisory Action received by the

Appellant on August 3, 1998. An Amendment cancelling claims 9 and 10 accompanies this appeal brief.

(5) SUMMARY OF THE INVENTION

Claims 11-15 and 19-22 are drawn to a nucleotide molecule encoding SR-BI, a protein normally expressed on the surface of certain cells, principally in the liver and tissues involved in steroidogenesis, which binds native as well as acetylated low density lipoprotein ("LDL"). Based on its binding affinity for acetylated LDL, the protein was classified originally as a scavenger receptor protein. SR-BI has subsequently been determined to be the only known receptor to mediate cholesterol transport - that is, uptake and transport through cells. Claims 44-47 are drawn to a method for screening of compounds altering binding of LDL or modified LDL to the SR-BI protein encoded by the nucleotide molecule of claim 11. Claim 48 is drawn to a method for removing LDL from a patient's blood by binding to immobilized SR-BI. Claim 49 is drawn to a method for inhibiting uptake of lipids and lipoproteins by adipocytes by inhibiting binding of the lipids or lipoproteins to the SR-BI protein encoded by the nucleotide molecule of claim 11. Claim 50 is a method for screening of patients with SR-BI having abnormal binding function.

Scavenger receptor proteins are described in the application at pages 1-3, and their structure shown in Figures 1A and B. SR-BI has a very different structure than the other scavenger receptor proteins. However, it is classed as a scavenger receptor protein since it binds

modified LDL (Figure 3A) as well as a number of other ligands (Figure 3B) (page 16, line 5, to page 17, line 8, and page 22, line 22, to page 24, line 21 and page 24, line 35-page 27, line 21). Its binding activity is similar to, but distinct from, other scavenger receptor proteins since it binds native LDL (Figure 3B) and high density lipoprotein ("HDL") (see page 19, lines 9-28, and Figure 8A). SR-BI's binding activity is also distinct from the similar but different molecule CD36 (page 27, line 34, to page 29, line 12; also, compare Figure 3B and Figure 4B and see Figure 5).

SR-BI was cloned from a hamster cell line by screening for scavenger receptor proteins by binding to acetylated LDL (page 22, line 23, to page 24, line 21). Once the cells had been isolated and the binding activity demonstrated by hybridization studies not to be due to SR-A (page 24, line 22, to page 25, line 20); a cDNA encoding a previously unknown scavenger receptor was obtained by screening of an expression library for binding of acetylated LDL (page 25, lines 21-34). A plasmid containing this cDNA was transfected into other cells and shown to express a protein binding acetylated LDL (page 26). The hamster SR-BI cDNA was then sequenced, analyzed and used as a hybridization probe to obtain a cDNA encoding the murine SR-BI (page 27, lines 22-32). Cells transfected with the isolated cDNA were further characterized for their binding activity (page 28, line 12, to page 31, line 10). Various tissues were then screened for expression of SR-BI and it was demonstrated to be preferentially expressed in steroidogenic tissues (page 31, line 11, to page 33, line 5). As noted at page 33, lines 34-36, SR-BI was believed to be responsible for cholesterol delivery to steroidenic tissues

and liver. SR-BI is now known to be the only protein known to be involved in cholesterol transport.

The claims are drawn not only to the nucleotide molecules encoding SR-BI, but assays for screening of binding to SR-BI. The specification exemplifies direct and competitive binding studies for use in the claimed methods as described above. More specific information on screening of patient samples and hybridization probes is provided at pages 40-41 and 43-50.

(6) ISSUES ON APPEAL

The issues present on appeal are

(1) whether claim 19 is adequately described in the specification pursuant to 35 U.S.C. §112, first paragraph;

(2) whether claims 11-13, 15, 19-22, and 44-50 are enabled under 35 U.S.C. § 112, first paragraph,

(3) whether claim 49 is adequately described under 35 U.S.C. §112, first paragraph;

(4) whether claims 44 to 50 are incomplete under 35 U.S.C. §112, first paragraph;

(5) whether claims 11-15, 19-22, and 44-50 are vague and indefinite under 35 U.S.C. § 112, second paragraph, for referencing "SR-BI", "hybridizing", and "or a degenerate variant thereof";

(6) whether claims 11, 12, 15, 19, and 20 are disclosed under 35 U.S.C. § 102(a) by Calvo et al., J. Biol. Chem. 268(25) 18929-18935 (1993), and

(7) whether claims 13, 14, 19, 21, and 22 are obvious under U.S.C § 103 over Calvo et al., J. Biol. Chem. 268(25) 18929-18935 (1993).

(7) GROUPING OF CLAIMS

Appellants submit that the claims do not stand or fall together.

Claims 11-15 and 19-22 are drawn to an isolated nucleic acid molecule that encodes a type BI scavenger receptor protein, alone or in combination with an expression vector or cell for expression thereof. Claims 12, 21, and 22 are drawn to the nucleic acids of claim 11 that are expressed in either adipocyte cells, lung cells, or liver cells and the expression vectors that encode the molecules of claim 11. Claim 13 is drawn to the molecule of claim 11 that hybridizes to SEQ ID No. 3 under stringent conditions. Claim 14 is drawn to the molecule of claim 13 having the sequence of SEQ ID No. 3 or a degenerate variant thereof.

The dependent claims further limit and define molecules of claim 11, and each different limitation must be examined separately to the extent it narrows the scope and number of molecules encompassed by each claim.

For example, claim 15 is drawn to the molecule of claim 11 encoding a protein with the amino acid sequence shown in SEQ ID No. 4. It is clearly different in scope from claim 11 and represents an extremely small and defined class of SR-BI proteins.

Claims 44-47, drawn to a method for screening for compounds altering binding of LDL or modified LDL to a scavenger receptor protein, which does **not** require the nucleic acid

molecule of claims 11-15 and 19-22.

Claims 44 and 47 are drawn to a method for screening for a compound which alters the binding of scavenger receptor protein type BI as defined by the application. The method involves providing reagents for use in an assay for binding of low density lipoprotein or modified low density lipoprotein to the scavenger receptor protein, adding the compound to be tested to the assay, and then determining if the amount of modified low density lipoprotein or low density lipoprotein which is bound to the scavenger receptor protein is altered as compared to binding in the absence of the compound to be tested.

Claim 45 is drawn to the method of claim 44 but limits the assay for binding to a cell expressing the scavenger receptor protein, *which occur naturally and for which sources are identified in the application.*

Claim 46 is drawn to the method of claim 44 but further limits the compound to one that is selected from a library of compounds by randomly testing for alteration of binding.

Claim 48, drawn to a method for removing LDL from blood by reacting the blood to SR-BI protein, which does **not** require the nucleic acid molecule of claims 11-15 and 19-22. The blood is reacted with immobilized scavenger receptor protein type BI under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

Claim 49, drawn to a method for inhibiting uptake of lipoprotein or lipids by adipocytes by inhibiting binding of the lipoprotein to the SR-BI, which does **not** require the nucleic acid molecule of claims 11-15 and 19-22. The method involves selectively inhibiting binding of

lipoprotein to the scavenger receptor protein type BI under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

Claim 50, drawn to a method for screening patients for abnormal scavenger receptor protein or function by determining the presence, quantity or function of the SR-BI and comparing it to that present in normal cells, which does **not** require the nucleic acid molecule of claims 11-15 and 19-22.

Since each method requires different reagents, different method steps, different starting materials, and different motivation to combine as appellants' have done, the method claims must be analyzed separately.

(8) ARGUMENTS

a. The Claimed Subject Matter

There are actually multiple inventions defined by the claims. As discussed above under grouping of the claims, the claims are broadly divided into two groups: claims drawn to isolated nucleic acid molecules that code for scavenger receptor proteins that are characterized by a defined binding affinity and methods for screening based on binding of the scavenger receptor proteins. The methods can be further divided based on the reagents and steps by which a particular object is achieved: (1) screening of compounds altering binding of SR-BI to LDL or modified LDL; (2) removing LDL from blood by reacting the blood with immobilized SR-BI; (3) inhibiting uptake of lipoproteins or lipids in adipocytes by inhibiting binding of the LDL to

SR-BI; and (4) screening patients for abnormal SR-BI by measuring the amount or function of the SR-BI and comparing it to SR-BI in normal cells.

SR-BI is defined in the specification based on its three dimensional structure (see Figure 1B), amino acid sequence (SEQ ID Nos. 4 and 8), and binding activity (binds native LDL, modified LDL, and HDL). It has been demonstrated to be unique in all three areas, and to exhibit complete identity in three dimensional structure and functional activity across all species and have very high sequence identity between species (see, for example, the printouts of the amino acid sequences for the SR-BI cloned from hamster, rat, mouse, human and cattle, showing the similarity between the proteins, as well as the hamster (SEQ ID NO 4) and murine (SEQ ID NO 8) amino acid sequences provided in the application). Further, from the latter, one can readily determine which amino acids are conserved between species and critical function. Moreover, it is possible to detect SR-BI from one species with the DNA from another. As described in the application, Northern blot analysis of murine tissues was conducted using the hamster DNA), to show that SR-BI is most abundantly expressed in fat and is present at moderate levels in lung and liver. One skilled in the art, reading the phrase "SR-BI" or "scavenger receptor protein type BI" would know that this referred to a very particular type of protein. Based on the tissue expression data in the application, as well as the binding data, one skilled in the art would also know that it is involved in lipid transport, that it is highly unusual because it binds both native and modified LDL, that it binds cholesterol and HDL, and that it plays a role in steroidogenesis and transport of cholesterol to the liver, unlike any other

scavenger receptor protein.

SR-BI, and the nucleic acid molecules encoding SR-BI, were not known to exist prior to cloning and expression of the SR-B1 receptor from hamster cells by appellants. Appellants obtained the DNA encoding the receptor while conducting studies to extend the analysis of the structure and function of mammalian modified lipoprotein scavenger receptors, using standard screening assays for lipoprotein binding by proteins expressed from DNA obtained from a variant Chinese hamster ovary cell line (Var-261, which also expresses an apparently novel polyanion binding scavenger receptor distinct from SR-BI). Since many proteins are known to bind to lipoproteins, especially modified lipoproteins, the protein obtained from the Chinese hamster ovary cell line was characterized based on its binding specificity and compared to other known receptors, such as SR-A and CD36, a plasma membrane glycoprotein present in a restricted number of cell types, including platelets, monocytes, and some types of endothelial, epithelial, and melanoma cells. Not only is the binding specificity of these two proteins different, the cDNA encoding SR-BI yields a predicted protein sequence of 509 amino acids which is only approximately 30% identical to those of the three previously identified CD36 family members.

SR-BI is an important, highly conserved protein, playing a critical role in cholesterol transport. Once one has the protein and the isolated DNA encoding protein, from any species, it is possible to make antibodies to the protein or hyridization probes which can be used to screen patients or tissues for expression of SR-BI in levels or with function that is not normal (claim

50); it can be used as a target in a screening procedure for drugs which bind to SR-BI to alter lipid or lipoprotein uptake or transport (claims 44-47 and 49); and it can be immobilized and used to remove LDL from a patient's blood (claim 48). None of these methods require any reagents not explicitly described and demonstrated in actual examples in the application.

b. Rejections Under 35 U.S.C. § 112, first paragraph.

The claims have been rejected under 35 U.S.C. §112, first paragraph, on the basis that the claims are not enabled nor definite. 35 U.S.C. §112, first paragraph, provides in relevant part:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, "

Each specific rejection under this paragraph is discussed separately below.

i. Claim 19 is enabled

Claim 19 defines a nucleotide molecule encoding a human SR-BI. Appellants acknowledge that the nucleotide sequence for this molecule is not recited in the application. However, while the examiner goes into a great deal of discussion regarding issues of species versus genus, acknowledging that applicants have disclosed a species (actually two, the species from hamster and the species from mouse), he states at page 3 of the Office Action mailed March 19, 1998, that "Because the instant application does not provide a written description of those material properties which distinguish "a human scavenger receptor" from any other mammalian

scavenger receptor, a practitioner of the art cannot produce the claimed nucleic acid to the exclusion of a nucleic acid encoding any other mammalian scavenger receptor." This statement is patently incorrect and nonsensical.

First, appellants are not claiming any human scavenger receptor; they are only claiming SR-BI, which is characterized as having a defined structure, amino acid sequence as found in two different species, increased expression in certain types of cells, and a unique binding activity. No other scavenger receptor binds both native and acetylated LDL. No other scavenger receptor binding both native and acetylated LDL can be obtained by routine screening of tissues using a probe from either of the two nucleotide sequences from hamster and mouse that are provided. Appellants demonstrate that it is possible to use a probe from one species to identify DNA encoding the same protein from a second species, as discussed above. Appellants are aware of no unique features of human SR-BI that makes it necessary to define human SR-BI any differently than they have for any other species. Indeed, as demonstrated from abstracts from a few subsequently published papers, the human SR-BI is extremely similar in amino acid sequence and identical in binding activity, binding both native and acetylated LDL, which appellants have demonstrated can be routinely used to obtain DNA encoding an SR-BI protein from species other than the species for which nucleotide sequence is known.

Furthermore, the issue of description is adequately met simply by constructively reducing the material to practice (*Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991)). The Court in *Vas-Cath Inc. v. Mahurkar* stated, "Whether the disclosure of the

application relied upon reasonably conveys to the skilled artisan that the inventor had possession at the that time [i.e., when the application was filed] of the later claimed subject matter." As long as the subject matter was described in the specification as it was claimed, the description requirement is met. Applying this standard, the human homologue as claimed in claim 19 clearly meets the description requirement.

In so far as the Examiner is relying on *Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d. 1398 (CAFC 1997) as the basis for this rejection, Appellants note that *Regents of U.C.* is not applicable since the claims and underlying specification here are not analogous to the facts there. The Court in *Regents of U.C.* relied on the fact that the description of example 6 in the patent at issue prophetically described obtaining a cDNA sequence from the **protein** sequence of the human protein. This is completely different than the situation here, where the specification relies on the use of the homologous cDNA as a probe, not a degenerate sequence obtained by reverse translation of a protein sequence. This difference is absolutely critical because the court in *Regents of U.C.* relied on their own precedence of *In re Deuel* 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (1995). The court stated, "A prior art disclosure of the **amino acid sequence** of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences encoding for the protein." In relying on the relationship of amino acid sequence to nucleic acid sequence, *Regents of U.C.* is limited to protein-to-DNA situations. It should be noted that the court in *Regents of U.C.* did not

specifically address (and thus, did not overrule) the standard that has been accepted for the description requirement for the last 125 years, most recently explicated in *Vas-Cath Inc. v Mahurkar*. Notwithstanding the above, it is noted that only decisions handed down by an *en banc* panel of the Federal Circuit are sufficient to overrule previous case law. In this respect, the decisions of the Federal Circuit in *Eli Lilly* and its progenitor cases do not overrule the longstanding positions taken by the courts on the description requirements. (*Vas-Cath Inc. v Mahurkar).*

In summary, one skilled in the art to which claim 19 pertains, cloning of a scavenger receptor protein, would have been able to obtain a nucleotide molecule encoding human SR-BI with no more than routine experimentation, as of the priority date of this application (June 23, 1994), based on the disclosure by appellants using commercially available reagents and standard techniques.

ii. Claims 11-13, 15, and 19-22 are enabled

Claims 11-13, 15, 19-22 and 44-50 were rejected under 35 U.S.C. §112, first paragraph, as non-enabled for a nucleic acid encoding a scavenger receptor protein lacking one of the amino acid sequences that are disclosed in SEQ ID NOs 4 (hamster SR-BI), 6 (Drosophilia SR-C) and 8 (murine SR-BI).

First, it should be noted that SEQ ID No. 6 does not encode SR-BI, but a totally distinct protein, SR-C, having a very distinct structure, amino acid sequence, and function, which is not being prosecuted in this application.

This rejection is incorrect because it fails to analyze the claims as a whole, and the claims individually. For example, claim 15 is drawn to an SR-BI having the *exact amino acid sequence* of SEQ ID NO. 4. The rejection also fails to take into consideration the level of skill in the art and the other modifying limitations describing the SR-BI, and the meaning of the claim language as read in view of the definitions in the specification. For example, claim 11 also requires the protein to bind LDL and to acetylated LDL; claim 12 requires that the protein be expressed in adipocytes, lung cells and liver cells (all shown in the specification to express high levels of SR-BI); claim 13 requires hybridization under stringent conditions; claim 14 requires the sequence of SEQ ID No. 3 or a degenerate variant thereof (which can be determined by comparison of SEQ ID NO 3 and 7); and claim 19 requires the protein be a human SR-BI.

The standard for making a rejection based on 35 U.S.C. § 112, first paragraph, is articulated in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (see also MPEP § 2164.01 and 2164.04). Initially, the Patent Office must accept the objective truth of statements made in the specification. If such statements are to be called into question, the Patent Office is burdened with providing evidence or convincing argument why those of skill in the art would doubt the statements. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). This burden has not been met.

While 35 U.S.C. § 112 does not recite the words "undue experimentation", this is the standard that is to be applied when assessing whether an application enables the claimed invention. *In re Wands,* 858 F.2d 731, 737 8 USPQ2d 1400 (Fed. Cir. 1988).

A determination of undue experimentation is a conclusion based on weighing many factors, not just a single factor. Many of these factors have been summarized in *In re Forman,* 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) and set forth in *In re Wands.* They are: (1) The quantity of experimentation necessary (time and expense); (2) The amount of direction or guidance presented; (3) The presence or absence of working examples of the invention; (4) The nature of the invention; (5) The state of the prior art; (6) The relative skill of those in the art; (7) The predictability or unpredictability of the art; and (8) The breadth of the claims.

While it is true that the specificity of nucleic acid interaction, or hybridization, can be affected by the conditions that the hybridization occurs under, those of skill in the art know how to perform hybridization experiments that lead to specific gene recognition of homologues, and the present application **specifically describes** how to do this for a SR-B1 cDNA. For example, on page 18, line 27 to page 19, line 6, there is an explicit description of a hybridization procedure in which the isolated hamster SR-B1 cDNA is used to produce a 600 base probe (derived from a BamHI restriction digest of the DNA shown in SEQ ID No. 3) which is used to probe different cell types from murine tissues and from 3T3 cells. The hybridization and washing conditions were done at 42° C and 50° C respectively using the well known conditions described by Charron et al. *Proc. Natl. Acad. Sci.* 86 2535-2539 (1989). Performing the hybridization analysis as described in the application clearly shows that a single predominant band of 2.4 kb was abundant in fat and present in moderate levels in lung and liver (page 31:line 11 to page 32:line 24). While the 600 base probe derived from the hamster scavenger receptor type B1 cDNA hybridizes

as a single gene sequence in mouse, a probe from CD36 has a different hybridization pattern, indicating that the hybridization assay described is sufficient to differentiate between CD36 and Appellants' nucleic acids encoding SR-B1 type proteins. This fact is significant since, as pointed out by the Examiner, other non-SR-BI genes are closely related in sequence to hamster and human SR-BI sequence (see Calvo et al.). This indicates that while CD36 and SR-B1 are related proteins (both members of the CD36 superfamily), they are not so related as to be considered homologues with each other and one skilled in the art would not interpret a reference to SR-BI as being the same as a reference to CD36; although CD36 is also excluded from the scope of the claim due to the binding specificity requirement: as shown in Figure 5, graphing competitive binding of acetylated LDL to either SR-BI or CD36 in the presence of native LDL, SR-BI binds native LDL and CD36 does not.

In summary, one skilled in the art, reading the claim which includes not only the phrase "hybridization" in conjuction with a defined sequence as wellas the binding specificity of the SR-BI would know exactly what was defined by the claims. The claims are therefore definite, and enabled, by the specification.

Claims 11-13, 15, 19-22 and 44-50 were also rejected under §112, first paragraph, on the basis that the "claims encompass nucleic acids encoding proteins whose amino acid sequences have been substantially altered from their natural forms whereas the instant specification does not provide the guidance that is required to produce such nucleic acids in a predictable manner."

First, its should be noted that the mere fact that claims encompass embodiments that are

not explicitly described, nor exemplified, does not render the claims non-enabled. In fact, inclusion of some embodiments that are even inoperative would still not render the claims non-enabled.

As articulated by this Board in *Ex parte Mark*, 12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int'f 1989), "When it is considered that the claims remaining on appeal all require that the mutein produced retain the biological activity of the native protein, we consider the disclosure of this application to be enabling . . . The fact that a given protein may not be amenable for use in the present invention in that the cystein residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a give protein are needed for retention of biological activity." 12 U.S.P.Q.2d at 1906-1907.

As applied to the claims here on appeal, one skilled in the art can obtain starting material merely by reference to the application before him. He can readily compare the amino acid sequences for the hamster and mouse SR-BI proteins and determine which amino acids are conserved and which are not. He can enter the amino acid sequence into computer programs that are commercially available and look at the resulting structure, to determine which amino acids are located at critical regions. Even if an amino acid is changed, intentionally or accidentally or by nature, it would require no more than routine effort to screen for activity. The assays to screen for binding activity are detailed in the application and the expected ranges actually demonstrated. The minimal nature of the experimentation required to obtain these proteins is

demonstrated by how appellants, with no knowledge of the existence of this protein nor its activity, were able to screen *an entire expression library* for activity, as they did to originally isolate the SR-BI from hamster cells. See in particular the studies reported at page 36, in which *3500 clones were screened initially for activity, then subdivided into 18 subpools of 350 clones which were transfected into cells and screened again.* Appellants also demonstrated that they were able to obtain the mouse SR-BI DNA using the hamster DNA, with no more than routine effort. With the sequences of SR-BI proteins from two different species, and their activity profiles in hand, as well as the requirement that the nucleic acid hybridize to these known sequences, it would only require routine testing to determine which molecules are encompassed by the claims.

The CCPA first addressed the issue of protein variants in *In re Fisher*, 427 F.2d 833 (CCPA, 1970). Integral to this holding was the court's reliance on the knowledge of one of ordinary skill in the art, and the lack of a showing that one of ordinary skill in the art could obtain sequences other than 39 amino acids long. The court stated,

> The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and *there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation.* As for Appellant's conclusion that the 25th to 39th acids in the chain are unnecessary, *it is one thing*

> *to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids*; it is quite another thing when they are not able to do so.
>
> Id. at 836. (emphasis added).

It is clear that the court was placing great emphasis on what one of ordinary skill in the art could have hoped to make or obtain. This decision was handed down in 1970, on an application filed November 29, 1960, claiming priority from an application filed June 9, 1954. The priority application was filed one year after Watson and Crick determined that the structure of DNA was a double helix (Watson and Crick *Nature* 171, 964-967 (1953)). It would still take seven years of research before scientists even knew that there was a triplet code between a DNA sequence and a protein sequence (Crick et al. *Nature* 192 1227-1232 (1961)). It is not reasonable to assume that a holding, based on an application filed in 1954, prior to the advent of biotechnology, is controlling on biotechnology itself. The court in *In re Fisher* very likely correctly held that "one could not make or obtain", without undue experimentation, a protein with less than 39 amino acids . . . *in 1954*. The court just as correctly noted though that if one of ordinary skill in the art could have made or obtained such a protein then the holding would have been very different. *Unlike this case*, appellants have demonstrated that one of ordinary skill in the art of cloning *in 1994* can obtain other nucleotide molecules encoding SR-BI with the requisite activity, without undue experimentation.

The court in *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200 (Fed. Cir.

1991) relied heavily on the holding in *In re Fisher* to find a claim drawn to a large number of non-natural Erythropoietin (EPO) analogs invalid for failing to meet the requirements of 35 U.S.C. 112. The court focused on the number of possible analogs that were encompassed by the claim **and** on the uncertainty held by the applicant as to which analogs, already produced, possessed the activity. The trial court relied on expert testimony which provided that "Amgen is still unable to specify which analogs have the biological properties set forth in the claim." *Id.* at 1213. The Federal Circuit chose to focus on the making and using of the DNA sequences, which produce the protein which has the biological activity, rather than the biological activity itself. While the *Amgen* court spoke positively of *In re Angstadt*, 537 F.2d 498, 502, which held that it is not necessary that a patent applicant test all embodiments of his invention, just that he provide a sufficient disclosure to enable one skilled in the art to practice the full scope of the claims, they stated that for claims based on DNA sequences a sufficient disclosure meant, "disclosing how to make and use enough sequences to justify grant of the claims sought." *Id.* at 1213. The court went on to state, "what is relevant *depends on the facts*, and the facts here are that Amgen has not enabled *preparation of DNA sequences* sufficient to support its all-encompassing claims." *Id.* at 1213. (emphasis added). Again, as in *In re Fisher*, the focus is on what Appellants, or one of ordinary skill in the art could do. The court focused on whether the preparation of the DNA sequences, within the scope of the claims, could *be prepared*. The application at issue was filed on November 30, 1984 and claimed priority to an application filed on December 13, 1983. Therefore, the "facts" relevant to the "preparation of DNA sequences" in the courts mind were

those that existed in 1983. This is almost four years prior to the advent of PCR. Chemical synthesis of DNA was still only able to routinely produce short oligonucleotides. In short, the two most important technological advances for the "preparation of DNA sequences" in a manner without "undue experimentation", PCR and highly efficient automated DNA synthesis, were still years away. A case decided based on the level of skill in the art *ten years earlier*, in a field changing almost hourly, cannot be used as a basis for a determination of what one skilled in the art would do as of 1994.

In *Hormone Research Foundation v. Genentech, Inc.* 904 F.2d 1558, 1568-69 (Fed. Cir. 1990). the court reversed a summary judgement for lack of enablement regarding claims directed to human growth hormone. The lower court had ruled that the alleged infringer had presented sufficient evidence indicating that the application was not enabled to merit summary judgement. (*Hormone Research Foundation v. Genentech, Inc.*, 708 F.Supp 1096 (N.D.Cal. 1988). The Federal Circuit remanded this issue for further adjudication because the lower court had failed to adequately address the analysis of *In re Hogan*, 559 F.2d 959 (CCPA 1977) and *United States Steel Corp. v. Phillips Petroleum Co.* 865 F.2d 1247 (Fed. Cir. 1989). In commenting on the relevance of these cases the *Hormone Research Foundation* court stated,

> It is unclear whether the high degree of potency and purity contemplated by the district court's analysis of enablement was influenced by the *potency and purity obtainable through recombinant DNA methodology*. Moreover, it is unclear from the

> record before us *whether that technology existed at the time the application was filed.* Further factual development as to the *state of the art at the date of the application* . . . is required for this court to review the enablement issues.
>
> *Id.*. at 1568-1569. (emphasis added).

The meaning and intent of the court is clear: one must assess the question of enablement in the light of the knowledge of one of ordinary skill in the art *at the time the application is filed.* In this case, Appellants have demonstrated one can skill huge numbers of molecules rapidly and without experimentation, and that it is possible to routinely obtain additional molecules encoding SR-BI merely by hybridization to one of the disclosed nucleotide molecules.

A central issue in the above cases is the level of predictability in the art. The question remains, however, as to what "unpredictability" means. For example, the court in *In re Vaeck* 947 F.2d 497 (Fed. Cir 1991) addressed the issue of unpredictability by stating, "we do *not* imply that patent applications in art areas currently denominated as unpredictable must never be allowed generic claims encompassing more than the particular species disclosed in their specification." *Id.* at 496. (emphasis contained in original). The court went on to state that "there must be sufficient disclosure . . . to teach those of ordinary skill how to make and how to use the invention . . ." *Id.* at 496. The question remains, what is a sufficient disclosure for an application that is in an "unpredictable" art? The clear answer given by the court was "the disclosure must adequately guide the art worker to determine, *without undue experimentation,*

which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496. (emphasis added). The court did **not** state, "without any experimentation," they stated "without undue experimentation". This means that a standard of "predictability" that excludes "all" experimentation is simply incorrect.

"Unpredictability" is often used as a sword by the PTO to slash the scope of a legitimate biotechnology claim. The sharpness and size of this sword, however, are unduly exaggerated because of the misapplication of what is and should be "predictable". In the area of functional variants, such as discussed in *In re Fisher* or *Amgen Inc., v. Chugai Pharmaceutical Co.,* the standard when assessing whether the specification enables one of ordinary skill in the art to make and use the claimed variants is whether it would require "undue experimentation" to determine which variants are functional. In the language of *In re Vaeck*, "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496.

The priority date for the application on appeal is June 23, 1994. By this time technologies such as PCR were highly developed and were routinely utilized to "prepare" DNA molecules which encoded for variants of known protein sequences. The importance of utilizing PCR cannot be overestimated with respect to the manipulation of DNA molecules, and specifically the insertion, deletion or substitution of DNA sequences which lead to changes in the amino acid sequence of a protein. The specification contains ample description of recombinant DNA methods that enable one of ordinary skill in the art to make SR-B1 receptors with varied

amino acids. For example, on page 51 the subsection entitled "Preparation of Receptor Protein Fragments" describes numerous methods including cleaving the protein with various proteases, expression of the altered protein from a recombinant DNA molecule, and even chemical synthesis of the desired protein fragment. On page 52:lines 14-18 the specification states, "These methods can be used to synthesize peptides having identical sequence to the receptor proteins described herein, or substitutions or additions of amino acids, which can be screened for activity."

The "preparation of the DNA molecules" encoding the variants of the sequences disclosed in SEQ ID NOs. 4 and 8 are fully enabled by the specification. Likewise, the assays to determine those variants that have the desired activity are readily described. The claims require that the nucleic acids encoding the SR-B1 receptor are capable of hybridizing with either SEQ ID. Nos. 3 or 7, and that it selectively binds to low density lipoprotein and modified lipoprotein. Assays for determining whether the modified DNA molecules hybridize to SEQ ID Nos. 3 or 7 are described at least from page 18:line 27 to page 19:line 6. As is indicated in these pages these methods were published in 1992, approximately three years before the priority date of the application. Clearly one of ordinary skill in the art would be able to practice techniques that were nearly three years old. In addition the application describes a number of assays that indicate whether a candidate SR-B1 protein binds low density lipoprotein and modified lipoprotein as required by the claims. For example, on page 19 there is a subsection entitled "HDL Binding Studies" and following this section is the description of "Phospholipid Binding

and Competition Assays." On page 21 there is yet another section entitled "Ligand Binding Assays" that discloses methods for determining if various low density lipoproteins and modified lipoproteins bind cells containing candidate SR-B1 receptors.

In the Advisory Action mailed August 3, 1998, the Examiner stated, "the issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record." As indicated above, the skill level of the artisan is high and the instant specification contains ample guidance for making and using the various protein variants. The issue of "predictability", "working examples", and "prior art of record" are dealt with below. The Examiner is clearly falling into the trap of interpreting "predictability" as prediction without **any** experimentation. This standard is absolutely inconsistent with the standard of "undue experimentation" set up in *In re Forman* and reiterated in *In re Wands*. The very word "predictability" is one of the factors to *determine* whether undue experimentation exists, not whether *any* experimentation should be commenced at all. It is a misapplication of the *Wands* standard to first ask the question "is it predictable which variant *a priori* has activity?", and then if the answer from the Examiner's position is "no" to forgo the undue experimentation analysis. This is clearly putting the proverbial cart before the horse. As Judge Rich illustrated in *In re Vaeck*, "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496. Clearly, "predictability" does not

supercede the standard of "undue experimentation" and the making of a DNA molecule encoding a variant of a SR-B1 receptor and testing this receptor for activity and characteristics required by the claims, in the technological world of 1994 is **not** undue experimentation.

The requirement by the Examiner that the specification contain working examples misconstrues the law and misconstrues the facts of the application. The legal standard does not require "working examples" in the specification, it is merely one of the factors which may be considered in a determination of undue experimentation. On page 5 of the Advisory Action mailed August 3, 1998, the Examiner states, "*Wands* now requires that one consider the number of working examples presented in the instant specification." This is false. The Federal Circuit explicitly stated in *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, "it is not necessary that a court review all the *Wands* factors to find a disclosure enabling" *Id.* at 1213. Thus, the specification does not require working examples to meet the correct standard which is undue experimentation.

Notwithstanding the above, the specification does provide working examples of SR-B1 proteins having different amino acid sequences that meet all of the requirements of the claims, the hamster homologue of SR-B1 and the murine homologue of SR-B1. While the applicant has not actually made "synthetic" variants of the SR-B1 protein, nature has provided the necessary evidence that there are protein variants of the hamster SR-B1 that exist which meet the limitations of the claims. There are numerous positions in the amino acid sequence of the murine homologue to the hamster SR-B1 that are "variant" from the hamster SR-B1 sequence.

The application teaches one how to make the protein variants, the application teaches one how to test the protein variants for activity, and the application teaches one that not every amino acid is required for function as required by the claims. The latter demonstration is what a working example can provide for an application, and this demonstration is provided by the fact that multiple homologues are disclosed.

The *Wands* factors do not require the "making of record prior art" as indicated by the Examiner at page 3 of the Advisory Action mailed on August 3, 1998. First, it is not required that all of the *Wands* factors be addressed to find that a claim does not require undue experimentation. Second, "making art of record" is not even one of the specific factors suggested. The nearest suggested analysis is "the state of the prior art." There is no requirement that all which is known to one of ordinary skill in the art be submitted to the Patent Office either in the form of the specification or in the art made of record.

Notwithstanding the above, the prior art made of record, while not explicitly required by the *Wands* factors, clearly supports the enablement of protein variants. For example, Cullen et al, "Use of Eukaryotic Expression Technology in the Functional Analysis of Cloned Genes," *Methods in Enz.* 152:684-704 (1987) describes numerous methods for producing eukaryotic expression vectors, such as those used in the present specification, to test specific DNA sequences for activity. Methods for domain swapping and protein mutagenesis were readily known to those of ordinary skill in the art and this is exemplified by Daugherty, et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting and rapid expression of a murine monoclonal antibody

directed against the CD18 component of leukocyte integrins," *Nucl. Acids Res.* 19:2471-2476 (1991).and Itakura et al., "Synthesis and use of synthetic oligonucleotides," *Ann. Rev. Biochem.* 53:323-356 (1984). Daugherty et al. describes methods for using the Polymerase Chain Reaction (PCR) to swap functional domains of a specific antibody between the murine and human homologues. Itakura et al. actually discusses site mutagenesis prior to PCR and describes this technology, in 1984, by saying "The once seemingly obvious limitations of this technique [referring to site directed mutagenesis] –availability of synthetic DNA and a knowledge of the nucleotide sequence of the target region—are no longer major factors." *Id.* at 343-344. Thus, in 1984, 10 years before the priority date of this application, the opinion of those of ordinary skill in the art was that the factors which arguably caused undue experimentation to make protein variants prior to 1984, "are no longer major factors" after 1984.

a. Claims 9 and 10 are fully enabled

Claims 9 and 10 have been cancelled by amendment with this Appeal Brief and are being pursued in a separate application and so are not argued here. However, there should be no rejection to these claims as lacking enablement. These claims are drawn to antibodies that bind scavenger receptor proteins and antibodies that bind scavenger receptor proteins which are detectably labeled are separately patentable.

b. Claims 12, 21, and 22 are fully enabled

Claims 12, 21, and 22 are drawn to the molecules of claim 11 with the added limitation that they are expressed in either adipocyte, lung, or liver cells. As discussed above, the

molecules of claim 11 are limited by the hybridization and modified lipocyte binding requirements of claim 11. Furthermore, the molecules of claims 12, 21, and 22 are separately patentable and enabled by the specification. Many of the binding studies were done with cells transfected with SR-B1 expressing molecules, like those of claim 11. For example, on page 29:line 26 to page 30:line 10 discusses a phospholipid binding experiment which used ldlA cells transfected with an haSR-B1 expressing plasmid. The results indicate that saturable binding takes place in the transfected cells, which indicates that these cells are at least expressing the haSR-B1 gene as is required by the claims. Northern blot hybridizations and blots with polyclonal antibodies to SR-BI were also performed showing that SR-BI is expressed in a variety of cell types (page 31-32)

c. Claim 13 is fully enabled

Claim 13 is separately patentable and fully enabled by the specification. Claim 13 further limits the molecules of claim 11 by requiring stringent hybridization conditions. An extensive discussion is present from page 40:line17 to page 41:line 19 on the parameters surrounding hybridization and stringent hybridization. Those of skill in the art are readily capable of adjusting temperature, base specificity, and salt concentrations (as discussed in the application) to create stringent hybridization conditions.

d. Claim 15 is fully enabled

Claim 15 is drawn to the molecule of claim 11 that specifically encodes the protein with the amino acid sequence shown in SEQ ID NO. 4. This claim is fully enabled by the

specification and is separately patentable because it further limits the molecules of claim 11 to those molecules having a specific sequence. Thus, claim 15 covers the nucleotide molecules that encode a specific protein, the protein defined by the amino acid sequence shown in SEQ ID NO. 4.

iii. Claims 44-50 are enabled

As discussed above, claims 44-50 are distinct from the claims drawn to nucleotide molecules. Each of these methods can be perfomed as described in the application as originally filed, without preparation of any nucleotide molecules encoding an SR-BI other than those explicitly exemplified.

The claimed methods in conjunction with the specification are absolutely clear and complete. One of skill in the art would be able to practice, without undue experimentation, the claimed methods. For example, the Examiner has singled out the recitation of "providing reagents for use in an assay for binding" in claim 44, as incomplete. The specification provides numerous examples of reagents for binding, such as AcLDL and M-BSA to name two. Page 28:line 15 to page 31:line 10 provides an extensive description of binding assays and binding reagents. Claims 44-50 are complete in their recitation of the necessary steps which set out the claimed methods. As outlined in *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971), the breadth of a claim is not to be equated with indefiniteness. The MPEP (2173.04) states, "If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims,

then the claims comply with 35 U.S.C. 112, first paragraph would be appropriate."

a. Claims 44 and 47 are fully enabled

Claims 44 and 47 are fully enabled by the specification and separately patentable. Claims 44 and 47 are drawn to methods for screening for compounds which alter the binding of the low density lipoproteins to the SR-B1 receptor. *These are not drawn to the compounds themselves.* The method comprises the steps of providing reagents for binding assays of low density or modified low density lipoproteins, adding the compound to be tested, and determining if the amount of low density or modified low density lipoprotein binding to SR-B1 is altered. The specification provides ample support for this method on pages 43 to 51.

b. Claim 45 is fully enabled

Claim 45 is fully enabled by the specification and is separately patentable. Claim 45 is drawn to the methods of claim 44 with the further limitation of requiring the assay include expression of the scavenger receptor protein in a cell, where the inhibiting molecule is a nucleic acid which alters expression of the scavenger receptor protein. On page 47, a section entitled, "Generation of nucleic acid regulators" describes methods to design and isolate nucleic acid molecules which inhibit the expression of a variety of proteins, including scavenger receptors.

c. Claim 46 is fully enabled

Claim 46 is separately patentable and fully enabled by the specification. Claim 46 is drawn to the method of claim 44 wherein the compounds tested are selected from a randomly screened library. This further limitation of the claim is fully supported in the application at page

45:lines 23-40. *In vitro* selection technologies and combinatorial chemistry approaches to the isolation of small molecule inhibitors are well known, and fully applicable to the isolation of molecules that inhibit SR-B1 binding to low density or modified low density lipoprotein.

d. Claim 48 is fully enabled

Claim 48 is fully enabled by the specification and is separately patentable. Claim 48 is drawn to the screening of patient blood samples and the removal of low density and modified low density lipoprotein from patient blood samples. Support for the limitations of this claim can be found on page 54:lines 9-15. Methods of attaching proteins to solid supports are described and well understood by those of ordinary skill in the art.

e. Claim 49 is fully enabled

Claim 49 was rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. This rejection is solely based on the "intended use" of the claimed compositions. The Examiner has asserted that the specification fails to teach how to "use" the claimed compositions. This rejection was made under 35 U.S.C. § 112, first paragraph, but really is nothing more than a rejection for lack of utility under 35 U.S.C. § 101. The claimed compositions and methods are fully enabled to make and use as required under 35 U.S.C. § 112, and have more than enough utility to meet the minimal standard required by the judicial interpretation of the utility requirement.

i. Legal analysis of the "utility" requirement under 35 U.S.C. §§ 101 and 112, first paragraph.

An invention must have utility. This requirement can be found in U.S.C. § 101 which states," Whoever invents or discovers any new and *useful* process or . . . composition of matter . . . may obtain a patent . . ." (emphasis added). This requirement is also implicitly found in 35 U.S.C. § 112 which requires the specification to provide a written description for "making and *using*" the claimed subject matter. (emphasis added).

Whether the utility requirement comes from 35 U.S.C. § 101 or 35 U.S.C. § 112, the standard to be applied is the same. *Ex parte Maas*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'f 1987). The *Maas* court stated, "the issue under 35 U.S.C. § 112 relating to an enabling disclosure is subsumed within the issue under 35 U.S.C. § 101 relating to patentable utility." Any analysis of a claim under 35 U.S.C. § 112, first paragraph relating to the use of the claimed subject matter, need only meet the standards of the utility requirement of 35 U.S.C. § 101 because if the claimed subject matter meets the utility requirement it is presumed to meet the enablement requirement.

To meet the utility requirement the invention must simply have a "practical utility" in the "real world sense." *Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA 1980). Any use which gives immediate benefit to the public is sufficient to be a "practical utility". *Id.* at 856. It is clear that for an invention to have "practical utility" it must be operative. However, to fail the utility

requirement the claimed subject matter must be "totally incapable of achieving a useful result."[1] *Brooktree Corp v. Advanced Micro Devices. Inc.*, 977 F.2d 1555 (Fed. Cir. 1992). An assertion of utility, even in the absence of evidence, is sufficient to meet the utility requirement unless the assertion is "incredible in the light of the art or factually misleading." *In re Citron*, 325 F.2d 1389 (CCPA, 1963).

The standard for utility does not change if the subject matter is pharmaceutical or therapeutic in nature. *In re Chilowsky*, 229 F.2d 457, 461-2 (CCPA 1956). "Knowledge of pharmacological activity is an obvious benefit to the public. . . . [A]dequate proof of any such activity constitutes a showing of practical utility." *Nelson v. Bowler* at 856. The Federal Circuit held that adequate proof of a pharmacological activity can be obtained by merely providing *in vitro* data which is suggestive of an activity *in vivo*. *Cross v. Iizuka*, 753 F.2d 1040 (CAFC, 1985). In *Cross v. Iizuka* the court stated, "Successful *in vitro* testing . . . [will lead to] . . . *in vivo* testing . . . thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility." *Id.* at 1051. Future testing in animals and future testing in humans, even if extensive, does not prevent a specification from meeting the utility requirement. The court stated in *In re Brana*, "Usefulness in patent law and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *In re Brana*, 51 F.3d 1560, 1568 (Fed.Cir. 1995). If the subject matter covered by

[1] See also *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980) ("In short, the defense of non-utility cannot be sustained without proof of total incapacity.")

pharmaceutical inventions requires future research and development, even after conception and constructive reduction to practice, when then is the utility requirement met? The Federal Circuit has answered this question: "The stage at which an invention in this field becomes useful is *well before* it is ready to be administered to humans." (emphasis added) *Id.* at 1568. The law does not explicitly state what is required to meet the utility requirement for any given pharmacological use because an analysis of utility is a fact based decision. *Ratheon v. Roper*, 724 F.2d 951, 956 (CAFC 1983). The law is explicitly clear, however, as to what pharmaceutical utility does **not** require. Pharmaceutical utility does not require human testing[2] or animal testing.[3] Pharmaceutical utility does not require a showing of therapeutic safety,[4] and it most certainly does not require a showing of efficacy.[5]

The standard for meeting the utility requirement under 35 U.S.C. § 101 is very low. The reasons for this are policy based because it is in the best interest of the public, the benefactors of the inventive material, to have the choice of when, how, and why to use the disclosed material.[6]

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[2]*In re Jolles*, 628 F.2d 1322 (CCPA, 1980); *In re Krimmel*, 292 F.2d 948 CCPA, 1961); *Cross v. Iizuka*, 753 F.2d 1040 (1985); and *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995)

[3]*In re Krimmel*, 292 F.2d 948 CCPA, 1961) and *Cross v. Iizuka*, 753 F.2d 1040 (1985)

[4] *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995) and *In re Irons*, 340 F.2d 974, 978 (CCPA 1965)

[5]See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); Ex parte *Jovanovics, 211 USPQ* 907 (Bd. Pat. App. & Inter. 1981)

[6]*In re Brana*, 51 F.3d 1560, 1568 (Fed.Cir. 1995) Not only does the public lose because of lost opportunity to utilize the invention, the public loses because of lost opportunity to benefit from further pharmaceutical research. Commenting on why the utility standard is what it is the *Brana* court stated, "Were we to require Phase II testing in

Failure to grant a patent because the Appellant allegedly fails to meet the utility requirement denies the public access to the information contained within the specification, and contradicts years of precedent directed towards protecting the public.

ii. Claim 49 is not a claim to an *in vivo* therapy as alleged by the Examiner.

Claim 49 is drawn to a method of inhibiting the uptake of lipoproteins and lipoprotein derivatives by adipocytes. Claim 49 is not drawn specifically to an *in vivo* method of inhibition or the treating of a patient through the method of inhibition. Nowhere in the language of claim 49, is there an element which requires the compounds to act in way that is "therapeutic." The application enables one of ordinary skill in the art without undue experimentation to make and use the claimed compositions. The application teaches one of ordinary skill in the art how to assay molecules for binding to the SR-B1 protein (page 28 :line 15 to page 31:line 10). The application teaches that those of ordinary skill in the art know that molecules which competitively bind to SR-B1 can inhibit lipoprotein binding and transport by adipocytes that express the SR-B1 receptor (page 43:line 30 to page 44:line 35).

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order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many areas such as the treatment of cancer."

This claim has been rejected solely because the Appellant has allegedly failed to provide "the route, duration and quantity of administration of that protein to a subject." (page 7, Advisory Action, mailed August 3, 1998). The Appellant does not have to teach how to "administer the protein to a subject" because administering the protein to a subject is not a limitation of the claim. Appellant is claiming a method of inhibition. Furthermore, the claimed method does not administer a protein to a subject. The method would, if used in an *in vivo* setting, require administering an inhibitory molecule, not the protein. The present specification meets the standard set forth in *In re Forman* and outlined in *In re Wands*.

Notwithstanding the above, ample guidance needed for the practice of the claimed method, as erroneously interpreted by the Examiner, appears on pages 43 to 54 of the specification. For example, on page 43:line 36 to page 44:line 22 the specification provides the exact element required by the Examiner -- a relationship between *in vitro* data and *in vivo* use. Because of the highly conserved nature of these proteins, the pathway from *in vitro* inhibition to *in vivo* use, via animal modeling, is highly predictive and successful. Methods of delivery of the inhibiting compounds and probable dosages are described on pages 53 and 54. Thus, the specification cannot be seen as providing "no guidance" and clearly meets the requirements of U.S.C. 35 §§ 101 and 112.

The courts have clearly held that in many circumstances *in vitro* data which is suggestive of *in vivo* function is sufficient to meet the utility requirement (*Cross v. Iizuka*), and that data in animals which are suggestive of human functionality are sufficient even if it never works in a

human (*In re Krimmel*). The specification provides guidance and motivation to test the compounds in an animal such as a mouse, because this would be predictive of results in a human (page 43:line 39 to page 44:line 2). This predictive power exists because of the close evolutionary relationship and high level of conservation between lower mammals and human forms of SR-B1 proteins.

The claims do not require any efficacy whatsoever for treating an "adipocyte" disorder. The legal standard does not require Appellant to show efficacy within a human.[7] This area is distinctly reserved for the Federal Drug Administration and is not a part of the patenting process.[8] For the reasons provided above, claim 49 meets the requirements of 35 U.S.C. 112, as outlined by *In re Wands*.

f. Claim 50 is fully enabled

Claim 50 is full enabled and separately patentable. Claim 50 is drawn to a method of screening patients to determine if the patients have abnormal levels of SR-B1 receptor or abnormally functioning receptor. The method comprises determining if there is a scavenger receptor present that hybridizes to either SEQ ID NOs. 3 or 7 and binds low density or modified low density lipoprotein, and then determining if the quantity present is similar to normal cells and if the function of the SR-B1 receptor is similar to the SR-B1 receptors of normal cells.

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[7]see *In re Langer*, 183 USPQ 288, 298 (CCPA 1974) (full scale clinical trials in humans...may be necessary to establish 'commercial usefulness' in this technology. However, development of a product to the extent that it is commercially salable in the marketplace is not required to establish 'usefulness')

[8]*In re Brana* 51 F.3d 1560, 1568 (Fed.Cir. 1995) "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws."

There are numerous assays for determining the amount of SR-B1 receptor present in a given cell. For example, from page 32:line 25 to page 33:line 5, methods using antibodies to recognize SR-B1 receptors are described. Those of ordinary skill in the art would readily know how to compare the amounts of SR-B1 protein in control cells to the cells of choice using these type of blotting techniques. The application also describes numerous binding assays to various low density and modified low density lipoproteins that characterizes SR-B1 function. One of ordinary skill in the art would know how to compare the binding capabilities of the control SR-B1 and the SR-B1 derived from the specific cell or patient being screened. Claim 50 is full enabled, and therefore, should be found valid by the Appeal Board.

c. Rejections Under 35 U.S.C. § 112, second paragraph

Claims 11-15, 19-22 and 44-50 were rejected under 35 U.S.C. §112, second paragraph, as indefinite. Specifically, claims 11-15, 19-22, and 44-50 were asserted to be vague for reciting on the basis "they recite the term 'scavenger receptor protein type BI' as a limiting element and the instant specification does not identify that property or combination of properties which is unique to and, therefore, definitive of a scavenger receptor protein type BI". Page 7, March 19, 1998, Office Action. Claims 11, 12, 15, 19-22 and 44-50 were asserted to be vague due to the use of the term "hybridizing". Claim 14 was rejected for the recitation of the term "or a degenerate variant thereof". Claim 21 was asserted to be vague based on the relationship in the claim between the molecule of claim 11 and the expression vector. Claim 22 was rejected for its reference to claim 21. Claim 46 was allegedly vague due to the recitation of "naturally occurring

or synthetic compounds" on the basis that this "implies that there is a third alternative." Page 9, March 19, 1998, Office Action.

i. The term 'scavenger receptor protein type BI is definite.

The term "scavenger receptor protein type BI" in claims 9-15, 19-22, and 44-50 is definite. Contrary to the Examiner's assertion that "The two elements 'encoding a protein X' and 'which hybridizes to a nucleic acid comprising the nucleic acid sequence of SEQ ID NO:## under stringent hybridization conditions' are two properties of a nucleic acid molecule which are not mutually inclusive nor is one a subset of the other," these properties do, in conjunction with the other limitations of the claims, distinctly claim the subject matter. It is axiomatic that nucleic acids define the proteins for which they encode. Furthermore, as the specification abundantly indicates, the nucleic acids of SEQ ID Nos. 3 and 7 do specifically and accurately define the scope of the claim. The issue of hybridization has been discussed exhaustively above.

In so far as the Examiner's assertion is directed to the function of the protein, the claims also include functional limitations such as "binding lipoprotein" which when coupled with the hybridization limitation do couple the cDNA to the protein that it encodes. The compositions and methods described in the present application define a new family of cDNAs which encode for a novel type of scavenger receptor protein, termed type BI. These cDNAs are related in that they hybridize to the sequences described in SEQ ID Nos. 3 and 7, and in that they encode for a novel type of scavenger receptor having the functional properties clearly defined in the claims and in the specification as a whole.

ii. "Or a degenerate thereof" is definite.

Claim 14 was rejected under 35 U.S.C. §112, second paragraph, for allegedly being vague and indefinite for reciting "or a degenerate thereof." The Examiner states, "Either the claimed nucleic acid encodes the amino acid Sequence ID NO:4 or it doesn't." The degeneracy of the DNA code is well known to those of skill in the art, and is understood to mean those DNA sequences which code for a given amino acid sequence. Claim 14 is not indefinite with respect to the degeneracy that is inherent in the genetic code.

iii. A claim can use inclusive terms.

Claim 46 is allegedly confusing because the term "naturally occurring or synthetic compounds" implies a third alternative. Appellants believe the Amendment filed December 29, 1997, addresses this issue. Specifically, claim 46 was amended to refer to "compounds", rather than "naturally occurring or synthetic compounds."

d. Rejection Under 35 U.S.C. § 102(a)

Claims 11, 12, 15, 17, 19 and 20 were rejected under 35 U.S.c. §102 as disclosed by Calvo, et al., *J. Biol. Chem.* 268(25), 18929-18935, September 5, 1993.

i. Legal analysis of 35 U.S.C. § 102

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991).

The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653

(Fed. Cir. 1986) (citations omitted).

ii. Legal analysis of 1.131 Declarations

37 C.F.R. § 1.131 states, in pertinent part,

> (a)(1) When any claim of an application . . . is rejected under 35 U.S.C. 102 (a) or (e), or 35 U.S.C. 103 based on . . . reference to . . . a printed publication, the inventor of the subject matter of the rejected claim . . . may submit an appropriate oath or declaration to overcome the . . . publication. The oath or declaration must include facts showing a completion of the invention in this country or in a NAFTA or WTO member country before . . . the date of the printed publication.
>
> * * *
>
> (b) The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice . . . .

The Applicant need only provide evidence that reasonably gives rise to an inference that the invention was completed before the reference date, in order to constitute a *prima facie* showing. No corroboration is required since the application process is *ex parte*. A Rule 131

affidavit is sufficient when it demonstrates that the Applicant has prior "possession" of that part of the invention disclosed by the reference, as is the case when a reference discloses a species falling within a claim to its genus. *See* Donald S. Chisum, **Patents** § 3.08[1][b] (Matthew Bender & Co. 1996). Possession in this context is shown by demonstrating conception, reduction to practice, and diligence--each as normally required in determining the date of invention. *See In re Mulder*, 716 F.2d 1542 (Fed. Cir. 1983).

In *In re Stempel*, 241 F.2d 755 (C.C.P.A. 1957), the court held that Applicant's affidavit under Rule 131 was not required to show priority with respect to the claimed genus, but only to the species disclosed by the cited reference, in order to remove that reference as prior art. The claims, both genus and species were drawn to chemical compounds. *Stempel* overcame the anticipation rejection by showing reduction to practice, prior to the effective date of the reference, of a species of the invention within the generic claims.

In *In re Tanczyn,* 347 F.2d 830 (C.C.P.A. 1965), the court qualified *In re Stempel*, stating that the *Stempel* doctrine did not apply to *partial* possession of the invention, as distinguished from *total* possession of a species within a genus claim. The *Tanczyn* application "did not involve a genus-species relationship." Id. at 833.

In *In re Clarke,* 356 F.2d 987 (C.C.P.A. 1966), the court extended the *Stempel* doctrine to the situation at issue in this application, that is where the Applicant's Rule 131 affidavit shows possession that is *not* of the entire invention nor of the part of the invention disclosed by the reference. The *Clarke* court held that the affidavit is sufficient to remove a reference where the

Applicant demonstrates possession of such "invention" as to make the entire claimed invention or the reference part obvious to one of ordinary skill in the art. The court stated,

> "[i]n an appropriate case an Applicant should not be prevented from obtaining a patent to an invention where a compound described in a reference would have been obvious to one of ordinary skill in the art in view of what the affiant proves was completed with respect to the invention prior to the effective date of the reference. . . . Thus, we think that in an appropriate case a single species could be sufficient to antedate indirectly a different species of a reference.".

The CCPA also has phrased the rule, "[w]hen that species of the generic invention which has been completed prior to the effective date of the reference would make obvious to one of ordinary skill in the art the species disclosed in the reference, the reference may be said to have been 'indirectly antedated.'" *In re Schaub*, 537 F.2d 509, 512 (C.C.P.A. 1976) (quoting *In re Ranier*, 390 F.2d 771, 773-74 (C.C.P.A. 1968)). The *Schaub* court stated that "[a]ppellants have made a *prima facie* case that the compound of the reference is obvious from the compounds which they have made prior to the date of the reference. Appellants' compound III is the next higher homolog of the reference compound II, . . ." Id. at 512-13.

There is little, if any, Federal Circuit case law on point. However, the rule established in *In re Clarke* apparently remains valid, as one somewhat recent, "unpublished" (i.e. not citable as

precedent) case seems to indicate. In *In re Rozmus*, 928 F.2d 412, 1991 WL 17232 (Fed. Cir.), the court stated that "[a]lthough Rozmus' [Rule 131] declaration showed reduction to practice of only a species of the generic invention, that alone is not fatal to his claim. A declaration proving a species is also sufficient to show possession of 'variations and adaptations which would, at the same time, be obvious to one skilled in the art.'" (quoting *In re Spiller*, 500 F.2d 1170, 1178 n.5 (CCPA 1974)).

Other cases discussing priority but which do not involve Rule 131 have stated, "[p]riority as to a genus may . . . be shown by prior invention of a single species, but the genus will not be patentable to an Applicant unless he has generic support therefor." *In re Zletz*, 893 F.2d 319, 323 (Fed. Cir. 1989); *see also Hoffman v. Schoenwald* 15 U.S.P.Q.2d 1512, 1514 (Bd. Pat. App. & Int'f 1990) ("Conception of a species within the genus constitutes conception of the genus for priority of invention purposes.").

iii. Claim 11, 12, 15, 19, and 20 are novel over Calvo et al., J. Biol. Chem. 268(25) 18929-18935 (1993).

Calvo, et al. reported isolation of a cDNA encoding a member of the CD36 superfamily. The protein was not physically isolated nor was the cloned DNA expressed, much less expressed on the surface of cells and shown to be functional, although a small piece non-functional portion (the carboxyl terminal region including residues 365-409) was expressed as a chimeric protein (page 18930). The function of the protein was not known, although its resemblance to CD36/LimpII was recognized based on the predicted similarities in structure and the authors

speculated that "on the basis of its structural homology to CD36 that CLA-1 could act as a receptor for extracellular products" (page 18934).

As demonstrated repeatedly by Appellants and discussed above, CD36 and SR-BI are *not* the same proteins nor do they have the same binding activity.

A Declaration under 37 C.F.R. §1.131, submitted in the parent application, U.S. Serial No. 08/265,428, filed June 23, 1994, which demonstrates that a cDNA and encoded protein defined by the claims in issue was conceived and reduced to practice prior to the publication of Calvo, et al. was submitted with the Response to An Office Action, mailed on December 29, 1997. Appellants cloned the gene, they expressed the protein, and they characterized the protein and showed its function, **prior to** Calvo's publication date.

The Examiner has stated that the Declaration under Rule 1.131 does not "demonstrate that the Applicant was in possession of the any information regarding a CLA-1 protein or CLA-1 gene from any animal other than hamster prior to the publication of Calvo et al." Appellants respectfully point out that this is not in fact true. Submitted with the Declaration is a printout obtained from the search of six databases (PDP, Swissprot, PIR, SPupdate, Genpept, GPupdate). This printout indicates that the Rat LimpII gene and the CD36 gene were among the genes with the highest homology to SR-B1. While these genes have been shown to be members of a different families within the superfamily of CD36 scavenger receptors than the SR-B1 proteins of the present application, for one of ordinary skill in the art they presented a nexus between the species described in the Declaration of Krieger and Acton and the genus which would include

the CLA-1 gene described in Calvo et al. The validity of these assertions is evidenced by the fact that the CLA-1 gene was isolated using primers derived from CD-36 and LIMP II, related but non-homologous proteins. Surely, the possession of the homolog of the CLA-1 protein, with the information that it fell within the CD-36 superfamily, is more information than Calvo et al. had when they cloned the CLA-1 gene, but not the homolog, from rat. The Appellants clearly were in possession of the genus of SR-B1 proteins and nucleic acid molecules that encode these proteins prior to the publication of Calvo.

Furthermore, the Examiner has stated, "There is no evidence in this Declaration that a nucleic acid probe encoding all or part of hamster CLA-1 was capable of hybridizing to mouse DNA or that a DNA encoding a murine cDNA had been isolated." This statement is incorrect. The latter is obviously wrong - SEQ ID NO. 7 *is* the nucleic acid sequence encoding the murine SR-BI. Moreover, the specification provides exactly the type of evidence the Examiner is looking for. For example, on page 18:line 27 to page 19:line 6 there is an explicit description of a hybridization procedure in which a 600 base probe of derived from the hamster SR-B1 cDNA is used to probe different cell types from murine tissues and from 3T3 cells. The results from these experiments clearly shows that a single predominant band of 2.4 kb was abundant in fat and present in moderate levels in lung and liver (page 31:line 11 to page 32:line 24). This data not only directly indicates an interspecies hybridization abundance, it indicates that this relationship is specific and successful because it recognizes the murine homologue in only those tissues that express it. The genus of the claims is described as cDNAs encoding Scavenger

Receptor Protein type B1, having specific functional properties, and includes the SR-B1 cDNA of the present application and the CLA-1 cDNA of Calvo et al. This genus is a subgenus of the genus of CD36 superfamily of scavenger receptor proteins which includes CD36 and LimpII.

To one of ordinary skill in the art there would have been more than sufficient motivation given the sequence homology data presented in the Declaration to utilize the information obtained from the novel hamster SR-B1 to isolate the human homologue based on the information provided in the specification and the general knowledge known in the art. As discussed below, this view is also held and argued by the Examiner.

iv. Claim 11 and 20 are novel

The sequences defined in claims 11 and 20 are novel because Calvo et al. has been antedated by the Krieger and Acton Rule 1.131 Declarations. Furthermore, the nature of the art is such that upon obtaining the sequences of the haSR-B1 and the murine SR-B1 those of ordinary skill in the art would have found it obvious to obtain the homologs to these nucleic acid molecules for the reasons outlined above.

v. Claim 12 is novel

Claim 12 is novel and separately patentable because Calvo et al. does not disclose, nor has Calvo et al. been alledged to disclose, the expression of the proteins encoded by the nucleic acid molecules described in claim 11 in adipocyte, lung, or liver cells. As discussed above, these limitations are fully enabled in the present application and render claim 12 novel over Calvo et al.

vi. Claim 15 is novel

Claim 15 is novel and separately patentable over Calvo et al. because Calvo et al. does not enable the protein sequence described in SEQ ID No. 4. In addition, as discussed above, Calvo et al. is not prior art for this sequence because of the antedating Rule 1.131 Declaration. Accordingly claim 15 is novel over Calvo et al.

vii. Claim 19 is novel

Claim 19 is novel and separately patentable over Calvo et al. because as discussed above the Rule 1.131 Declaration presented by Drs. Krieger and Acton indicates that the Appellants were in possession of the claimed subject matter prior to the publication of Calvo et al. Furthermore, as discussed above the inventive efforts of the Appellants made obvious the cloning of other SR-B1 homologs and therefore, the 1.131 Declaration is sufficient to antedate a "different species" within the genus.

e. Rejection Under 35 U.S.C. § 103

Claims 13, 14, 19, 21 and 22 are not obvious under 35 U.S.C. §103 over Calvo, et al. J. Biol. Chem. 268(25), 18929-18935 (1993).

i. Legal analysis of 35 U.S.C. § 103

The law is quite clear that, for the Patent Office to establish a *prima facie* case of obviousness of claimed subject matter, the prior art references relied upon must provide *both* a suggestion to make the claimed invention and a reasonable expectation of success. It is also clear that the whole field of the invention must be considered, including those publications which teach

away from the claimed invention. Particularly relevant to the matters under consideration here are the decisions of the Court of Appeals for the Federal Circuit in *In re Dow Chemical*, 5 USPQ2d 1529 (1988) and *In re Vaeck*, 20 USPQ2d 1438 (1991). The *Dow* Court noted that:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.... Both the suggestion and expectation of success must be founded in the prior art, not in the applicant's disclosure.
>
> In determining whether such a suggestion can fairly be gleaned from the prior art, *the full field of the invention must be considered*: for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.... Evidence that supports, rather than negates, patentability must be fairly considered.

5 USPQ 2d at 1531-1532 (Citations omitted, emphasis added).

In *In re Dow Chemical*, a combination of three components forming an impact resistant rubber-based resin was not found to be obvious based upon art disclosing the individual components. The court noted that the record had shown that the claimed combination had previously been made, *but did not produce the product desired.* "That there were other attempts, and various combinations and procedures tried in the past, does not render obvious the later

successful one.... Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness," *Id.* at 1531 (citations omitted). The Court found that none of the prior art cited by the Appellant and the PTO suggested that any process could be used successfully in this three-component system to produce the product having the desired properties. Further, the Court stated that evidence from an expert expressing skepticism as to the success of the claimed combination before these inventors proved him wrong should be considered. *Id.* at 1532.

ii. Claims 9, 10, 13, 14, 19, 21 and 22 are not obvious in view of Calvo et al. J. Biol. Chem. 268(25), 18929-18935 (1993).

As discussed above, the Krieger and Acton Declaration clearly shows that the Appellants were in possession of the cDNA and expressed protein prior to the date of Calvo et al. Therefore, Calvo et al. is antedated and not effective 35 U.S.C. § 103 art.

However, it cannot make obvious the genus where there was no expression of a protein, nor recognition of its properties.

Among the reasons that the Examiner has argued that it would be obvious to go from the Human CLA-1 gene described by Calvo et al. to the hamster homologue are: (1) CLA is described as being structurally analogous to LIMPII: (2) amino acid sequence were highly conserved between human and rat LIMPII; (3) the genes had sufficient similarity to permit the isolation of LIMPII; (4) an artisan would have concluded that any mammalian protein encoding CLA-1 would have been readily isolated by probing a DNA library, since the hamster, as well as rat, was routinely employed as a laboratory model for determining the physiological significance

of proteins of human origin since the scope of human experimentation is obviously limited, (5) and there was knowledge that there was homology between humans and rodents at the time. [Appellants note, in passing, that each and every one of these reasons, relied upon by the Examiner to support the "*prima facie*" case of obviousness to clone the hamster SR-B1 protein from the sequence information of the human CLA-1 protein were presented in the specification and Declaration in the present application, and one must assume that the Examiner may have used hindsight based on this Declaration to identify reasons why one would go from Calvo to what is claimed, rather than from what Appellants have demonstrated they conceived and reduced to practice, prior to Calvo, to arrive at what Calvo disclosed.]

Appellants do not understand how, in the light of the Declaration submitted, the Examiner can maintain that it was *prima facie* obvious to clone the hamster homologue of the human CLA-1 when Appellants have demonstrated possession of the hamster gene before the date of the publication of the human homologue CLA-1. Furthermore, in light of the Examiner's rejection of claim 19 under 35 U.S.C § 112 for an inadequate description of the human homologue of SR-B1, which implicitly relies on *Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d. 1398 (CAFC 1997), it is inconsistent to maintain a rejection which is contrary to the Examiner's only interpretation and reliance on case law. Appellants have distinguished themselves not only from *Regents of the University of California v. Eli Lilly and Company* (as discussed above), but also assert that in the light of the Declaration and the evidence provided in the specification, it would have been *prima facie* obvious to clone the

human homologue of SR-B1 from what Appellants had well prior to the publication by Calvo!

Appellants have demonstrated that they cloned and expressed the hamster gene encoding the claimed SR-BI proteins, and that the gene hybridizes to the murine gene, prior to publication by Calvo et al. Accordingly, Appellants conceived of and reduced to practice the claimed invention prior to Calvo et al. Therefore, the Declaration under 37 C.F.R. §1.131 should conclusively remove Calvo et al. as a reference, and the claims found patentable to Appellants.

iii. Claim 13 is not obvious

Claim 13 is not obvious in view of Calvo et al. and is separately patentable. Calvo et al. does not disclose "stringent hybridization" conditions which are required by claim 13 nor would it be obvious to choose these conditions.

iv. Claim 14 is not obvious

Claim 14, drawn to the hamster SR-BI sequence or degenerate variants thereof is not obvious in view of Calvo et al. and is separately patentable. As discussed above Calvo et al is antedated by the Rule 1.131 Declarations of Drs. Krieger and Acton.

v. Claim 19 is not obvious

Claim 19 is not obvious in view of Calvo et al. as discussed above with reference to antedating Calvo et al by the Rule 1.131 Declaration of Drs. Krieger and Acton.

vi. Claims 21 and 22 are not obvious.

Claims 21 and 22 are not made obvious by Calvo et al. and are separately patentable. Calvo et al. does not disclose the expression of the molecules of claim 11 in either adipocytes,

lung cells, or liver cells, nor for that matter, in any cell type. The Examiner has failed to meet his burden of extablishing a *prima facie* case of obviousness because there has been no showing that Calvo et al. ever expressed active, functional protein, knew what function to look for, or how to look for related proteins. In addition, there is nothing in Calvo et al. that would lead one to express the molecules of claim 11 in adipocyte, lung, or liver cells. Therefore, claims 21 and 22 are patentable over Calvo et al.

(9) SUMMARY AND CONCLUSION

In conclusion, claims 11-13, 15, 19-22, and 44-50 are enabled under 35 U.S.C. § 112, first paragraph, because the limitation of hybridization and specific lipoprotein binding limit the claims and in the present case variants of the claimed molecules are fully enabled. Claims 11-15, 19-22, and 44-50 are not vague and indefinite under 35 U.S.C. § 112, second paragraph. Claims 11, 12, 15, 19, and 20 are novel under 35 U.S.C. § 102(a) over Calvo et al., *J. Biol. Chem.* 268(25) 18929-18935 (1993) and claims 9, 10, 13, 14, 19, 21, and 22 are not obvious under U.S.C § 103 over Calvo et al., *J. Biol. Chem.* 268(25) 18929-18935 (1993) because the Rule 1.131 Declaration presented by Drs. Krieger and Acton show that the Appellants were in possession of the claimed subject matter prior to the publication of Calvo et al.

Appellants earnestly solicit the allowance of claims 11-15, 19-22, and 44-50.

Respectfully submitted,

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Date: February 11, 1999

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Patrea L. Pabst

Date: February 11, 1999

APPENDIX I: Claims on appeal

11. (amended) An isolated nucleic acid molecule encoding a scavenger receptor protein type BI which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, which hybridizes to SEQ ID Nos. 3 and 7.

12. (amended) The molecule of claim 11 expressed in cells selected from the group consisting of adipocytes, lung cells and liver cells.

13. (amended) The molecule of claim 11 hybridizing under stringent conditions to a molecule with Sequence ID No. 3.

14. (amended) The molecule of claim 13 having the sequence of Sequence ID No. 3 or a degenerate variant thereof.

15. (amended) The molecule of claim 11 encoding a protein with the amino acid sequence shown in Sequence ID No. 4.

19. (amended) The molecule of claim 11 which encodes a human scavenger receptor.

20. (amended) The molecule of claim 11 labeled with a detectable label.

21. (twice amended) A nucleic acid molecule comprising the molecule of claim 11 encoding the scavenger receptor protein and an expression vector.

22. (twice amended) A composition comprising a host cell suitable for expression of a scavenger receptor wherein the host cell comprises the nucleic acid molecule of claim 21.

44. (amended) A method for screening for a compound which alters the binding of scavenger receptor protein type BI, which is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 and which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, comprising

providing reagents for use in an assay for binding of low density lipoprotein or modified low density lipoprotein to the scavenger receptor protein,

adding the compound to be tested to the assay, and

determining if the amount of modified low density lipoprotein or low density lipoprotein which is bound to the scavenger receptor protein is altered as compared to binding in the absence of the compound to be tested.

45. (amended) The method of claim 44 wherein the assay includes a cell expressing the scavenger receptor protein and the compound is a nucleic acid molecule which alters expression of the scavenger receptor protein.

46. (amended) The method of claim 44 wherein the compound is selected from a library of compounds which are randomly tested for alteration of binding.

47. (amended) The method of claim 44 wherein the compound competitively inhibits binding of low density lipoprotein or modified lipoprotein having the characteristics of acetylated low density lipoprotein to the scavenger receptor protein.

48. (amended) A method for removing low density lipoprotein from patient blood comprising reacting the blood with immobilized scavenger receptor protein type B, wherein the

scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

49. (amended) A method for inhibiting uptake of lipoprotein or lipids by adipocytes comprising selectively inhibiting binding of lipoprotein to the scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

50. (amended) A method for screening patients for abnormal scavenger receptor protein activity or function comprising

determining the presence of scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, and

determining if the quantity present or the function of the receptor is equivalent to that present in normal cells.

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(9) SUMMARY AND CONCLUSION

Certificate of Mailing

Appendix I: Claims on Appeal

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SR-B1
hamster protein

NCBI Entrez **Protein QUERY** BLAST Entrez ?

Other Formats: GenPept Graphic

Links: MEDLINE DNA Related Sequences

>gi|562022 haSR-BI
MGGSARARWVAVGLGVVGLLCAVLGVVMILVMPSLIKQQVLKNVRIDPSSLSFAMWKEIPVPFYLSVYFF
EVVNPSEILKGEKPVVRERGPYVYREFRHKANITFNDNDTVSFVEHRSLHFQPDRSHGSESDYIILPNIL
VLGGAVMMESKSAGLKLMMTLGLATLGQRAFMNRTVGEILWGYEDPFVNFINKYLPDMFPIKGKFGLFVE
MNNSDSGLFTVFTGVQNFSKIHLVDRWNGLSKVNYWHSEQCNMINGTSGQMWAPFMTPQSSLEFFSPEAC
RSMKLTYHDSGVFEGIPTYRFTAPKTLFANGSVYPPNEGFCPCLESGIQNVSTCRFGAPLFLSHPHFYNA
DPVLSEAVLGLNPDPREHSLFLDIHPVTGIPMNCSVKLQISLYIKAVKGIGQTGKIEPVVLPLLWFEQSG
AMGGEPLNTFYTQLVLMPQVLQYVQYVLLGLGGLLLLVPVIYQLRSQEKCFLFWSGSKKGSQDKEAIQAY
SESLMSPAAKGTVLQEAKL

Save the above report in MACINTOSH TEXT format

NCBI *Entrez* **Protein QUERY** BLAST Entrez ?

Other Formats: GenPept Graphic

Links: DNA Related Sequences

>gi|4210542|gnl|PID|d1038274 scavenger receptor class B type I
MGVSSRARWVALGLGVLGLLCAALGVIMILMVPSLIKQQVLKNVRIDPSSLSFGMWKEIPVPFYLSVYFF
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MMGGKTLNTFYTQLVLMPQVLHYAQYVLLGLGGLLLLVPIIYQLRSQEKCFLFWSGSKKGSQDKEAMQAY
SESLMSPAAKGTVLQEAKL

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Other Formats: GenPept Graphic
Links: MEDLINE DNA Related Sequences

>gi|1167552 scavenger receptor class B type I
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RSMKLTYNESRVFEGIPTYRFTAPDTLFANGSVYPPNEGFCPCRESGIQNVSTCRFGAPLFLSHPHFYNA
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AMGGKPLSTFYTQLVLMPQVLHYAQYVLLGLGGLLLLVPIICQLRSQEKCFLFWSGSKKGSQDKEAIQAY
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human SR BI
(CLA-1)

NCBI Entrez **Protein QUERY** BLAST Entrez ?

Other Formats: GenPept Graphic

Links: MEDLINE Related Sequences

>gi|539636|pir||A48528 membrane glycoprotein CLA-1 protein long form precursor - h
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DPVLAEAVTGLHPNQEAHSLFLDIHPVTGIPMNCSVKLQLSLYMKSVAGIGQTGKIEPVVLPLLWFAESG
AMEGETLHTFYTQLVLMPKVMHYAQYVLLALGCVLLLVPVICQIRSQEKCYLFWSSSKKGSKDKEAIQAY
SESLMTSAPKGSVLQEAKL

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Other Formats: GenPept Graphic
Links: DNA Related Sequences

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>gi|2429348 scavenger receptor class B type I
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hamster
SR B1

NCBI Entrez **Nucleotide QUERY** BLAST Entrez ?

Other Formats: FASTA | Graphic

Links: MEDLINE | Protein | Related Sequences

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LOCUS       CGU11453     1788 bp    mRNA            ROD       26-JAN-1995
DEFINITION  Cricetulus griseus CD36-related class B scavenger receptor haSR-BI
            (haSR-bI) mRNA, complete cds.
ACCESSION   U11453
NID         g562021
KEYWORDS    modified lipoprotein receptor; oxidized low density lipoprotein;
            adipocytes.
SOURCE      Chinese hamster.
  ORGANISM  Cricetulus griseus
            Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
            Vertebrata; Eutheria; Rodentia; Sciurognathi; Myomorpha; Muridae;
            Cricetinae; Cricetulus.
REFERENCE   1  (bases 1 to 1788)
  AUTHORS   Acton,S.L., Scherer,P.E., Lodish,H.F. and Krieger,M.
  TITLE     Expression cloning of SR-BI, a CD36-related class B scavenger
            receptor
  JOURNAL   J. Biol. Chem. 269 (33), 21003-21009 (1994)
  MEDLINE   94342261
REFERENCE   2  (bases 1 to 1788)
  AUTHORS   Acton,S.L.
  TITLE     Direct Submission
  JOURNAL   Submitted (27-JUN-1994) Susan L. Acton, Biology, Massachusetts
            Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA
            02139, USA
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J Biol Chem 1999 Jan 1;274(1):41-7

Comparison of class B scavenger receptors, CD36 and scavenger receptor BI (SR-BI), shows that both receptors mediate high density lipoprotein-cholesteryl ester selective uptake but SR-BI exhibits a unique enhancement of cholesteryl ester uptake.

Connelly MA, Klein SM, Azhar S, Abumrad NA, Williams DL

Department of Pharmacological Sciences, University Medical Center, State University at Stony Brook, Stony Brook, New York, 11794-8651, USA.

[Medline record in process]

Scavenger receptor BI (SR-BI) mediates the selective uptake of high density lipoprotein (HDL) cholesteryl ester (CE), a process by which HDL CE is taken into the cell without internalization and degradation of the HDL particle. The biochemical mechanism by which SR-BI mediates the selective uptake of HDL CE is poorly understood. Given that CE transfer will occur to some extent from HDL to protein-free synthetic membranes, one hypothesis is that the role of SR-BI is primarily to tether HDL close to the cell surface to facilitate CE transfer from the particle to the plasma membrane. In the present study, this hypothesis was tested by comparing the selective uptake of HDL CE mediated by mouse SR-BI (mSR-BI) with that mediated by rat CD36 (rCD36), a closely related class B scavenger receptor. Both mSR-BI and rCD36 bind HDL with high affinity, and both receptors mediate HDL CE selective uptake. However, SR-BI mediates selective uptake of HDL CE with a 7-fold greater efficiency than rCD36. HDL CE selective uptake mediated by rCD36 is dependent on HDL binding to the receptor, since a mutation that blocks HDL binding also blocks HDL CE selective uptake. These data lead us to hypothesize that one component of HDL CE selective uptake is the tethering of HDL particles to the cell surface. To explore the molecular domains responsible for the greater efficiency of selective uptake by mSR-BI, we compared binding and selective uptake among mSR-BI, scavenger receptor BII, and various chimeric receptors formed from mSR-BI and rCD36. The results show that the extracellular domain of mSR-BI is essential for efficient HDL CE uptake, but the C-terminal cytoplasmic tail also has a major influence on the selective uptake process.

PMID: 9867808, UI: 99084987